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EXAMINER	
DUFFY, BRADLEY	

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1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,661	YAYON ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *30 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-10,15,18,20,22,31-35 and 38-44* is/are pending in the application.

4a) Of the above claim(s) *18,20,32-35 and 38-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-10,15,22 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 December 2003 and 20 April 2007* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice of Non-Compliant Amendment.

DETAILED ACTION

1. The amendment filed October 30, 2007 is acknowledged and has been entered. Claims 1, 6, 15, 31, 32, 38, 43 and 44 have been amended. Claims 4-5, 11-14, 17, 19, 21, 23-30, 36-37 and 45-49 have been cancelled.

2. Claims 1, 6-10, 15, 18, 20, 22, 31, 32-35 and 38-44 are pending in the application.

3. Claims 18, 20, 32-35 and 38-44 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 4, 2006.

4. Claims 1, 6-10, 15, 22 and 31 are currently under prosecution.

Response to Amendment

5. The amendment filed on October 30, 2007, is considered non-compliant because it fails to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). However, in order to advance prosecution, rather than mailing a Notice of Non-Compliant Amendment, Applicant is advised to correct the following deficiencies in replying to this Office action:

The amendment to the claims is non-compliant because it incorrectly and improperly lists the status of claims 18 and 20[1]. Notably, in the office action mailed July 25, 2007, these claims were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there

[1] See attached Notice of Non-Compliant Amendment

being no allowable generic or linking claim. Accordingly, claims 18 and 20 should be properly identified by the status identifier: (Withdrawn).

37 CFR § 1.121 (c) clearly states, "In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered)."

Applicant is reminded: Only the corrected section(s) of the non-compliant amendment must be resubmitted (in its entirety), e.g., the entire "Amendments to the claims" section of applicant's amendment must be re-submitted. 37 CFR § 1.121(h).

Priority

6. With regard to the issue of priority, Applicant has submitted at page 11 of the response filed October 30, 2007 that "the written description requirement and enabling requirement are irrelevant to priority data".

In response, the Examiner disagrees; as set forth in the previous office action, "[t]o receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994)". Accordingly, it is apparent that the written description requirement and enablement requirement are not irrelevant to establishing a priority date.

Therefore, since claims 1, 6-10, 15, 22 and 31 remain rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a

sufficiently enabling disclosure, the effective filing date of the instant claims is still deemed to be the filing date of PCT/IL02/00494, namely June 20, 2002.

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, Applicant's amendment and/or arguments filed October 30, 2007, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed July 25, 2007.

Grounds of Objection Maintained

Drawings

8. The objection to the drawings as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: 9B, 9C, 16B, 16C, 16D and 16E, is maintained. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

At page 11 of the response filed October 30, 2007, Applicant has traversed this ground of objection.

Applicant's arguments have been carefully considered but are not found persuasive for the following reasons:

In the response filed October 30, 2007, Applicant has argued that the specification recites "FIGS. 9A-9D" which includes figures 9B and 9C and recites "FIGS. 16A-16F" which includes figures 16B, 16C and 16D.

In response, while the disclosed ranges might include such figures, the references characters 9B, 9C, 16B, 16C, 16D and 16E are not *mentioned* in the recited disclosures.

Notably, 37 CFR 1.84(p)(5) states : Reference characters not mentioned in the description shall not appear in the drawings.

Accordingly, as the disclosure lacks the reference characters 9B, 9C, 16B, 16C, 16D and 16E, it is deemed to not properly mention these reference characters as required by 37 CFR 1.84(p)(5).

The Examiner notes that this objection would be obviate by amending the specification to recite "FIGS. 9A, 9B, 9C and 9D" instead of "FIGS. 9A-9D" and "FIGS. 16A, 16B, 16C, 16D and 16F" instead of "FIGS. 16A-16F".

Specification

9. The disclosure is objected to because of the following informalities:

(a) The objection to the specification because the use of improperly demarcated trademarks is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although it appears that Applicant has made a *bona fide* attempt to resolve this issue by appropriately amending the specification, an additional example of an improperly demarcated trademark appearing in the specification is noted, namely Taxol®; see, e.g., page 31, last paragraph.

Again, appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and

accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

(b) The objection to the specification because the Brief Description of the Drawings fails to comply with 37 CFR 1.84(p)(5) which requires every reference character to be described in the brief description, is maintained. In this case, the description of Figure 9 does not specifically mention Figure 9B and 9C and the description of Figure 16 does not specifically mention Figure 16B, 16C, 16D and 16E.

While Applicant submits that the specification recites "FIGS. 9A-9D" which includes figures 9B and 9C and recites "FIGS. 16A-16F" which includes figures 16B, 16C and 16D, this disclosure is not deemed to satisfy the requirements of 37 CFR 1.84(p)(5) for the reasons set forth in the above objection to the drawings.

(c) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

10. The objection to claims 7 and 8, as being drawn in the alternative to the subject of non-elected inventions, is maintained.

Starting at page 11 of the response filed October 30, 2007, Applicant has traversed this ground of objection.

Applicant's arguments have been carefully considered but are not found persuasive for the following reasons:

In the response filed October 30, 2007, Applicant submits that all the V_H and V_L combinations in claims 7 and 8 are drawn to the elected invention.

In response, as set forth at page 2 of the previous office action, "Applicant has elected to prosecute the invention of the Group XVI, claims 4-10, 15-22, and 31, drawn to a molecule comprising the antigen-binding portion of an isolated antibody comprising a V_H region of SEQ ID NO: 113 and V_L region of SEQ ID NO: 102 or a V_H–CDR3 region of SEQ ID NO: 24 and V_L–CDR3 region of SEQ ID NO: 25, which has an increased affinity for FGFR3 and which block constitutive activation of said FGFR3."

However, because Applicant has corrected a sequence compliance problem (see action mailed 1/12/2007); the elected invention, as now claimed, is a molecule comprising an antigen binding portion of an isolated antibody that comprises a V_H region of SEQ ID NO: 106 and a V_L region of SEQ ID NO: 95 or a V_H–CDR3 region of SEQ ID NO: 24 and V_L–CDR3 region of SEQ ID NO: 25, which has an increased affinity for FGFR3 and which blocks constitutive activation of said FGFR3. (see claim amendment filed April 20, 2007).

Accordingly, e.g., a molecule in claim 7 comprising the V_H and V_L combination of SEQ ID NO:96 and SEQ ID NO:85 does not read on the elected invention. Similarly, e.g., a molecule in claim 8 comprising the V_H–CDR3 region of SEQ ID NO: 8 and V_L–CDR3 region of SEQ ID NO: 9 does not read on the elected invention.

Appropriate correction is required.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. The rejection of claims 1, 6-10, 15, 22 and 31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

Beginning at page 12 of the response filed October 30, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As explained previously, claims 1, 6-10, 15, 22 and 31 are indefinite for the following reasons:

(a) The rejection of Claims 1, 6-10, 15, 22 and 31 as being indefinite because of the recitation of an "antibody which has an *increased affinity* for a fibroblast growth factor receptor 3" [italics added for emphasis] in claim 1, is maintained.

At page 12 of the response filed October 30, 2007, Applicant has argued that the specification defines *"increased affinity"* at paragraph [0135] of the published application as: "An antibody or a molecule of the present invention is said to have increased affinity for a RPTK if it binds a soluble dimeric form of said RPTK with a K_D of less than about 50 nM, preferably less than about 30 nM and more preferably less than about 10 nM, as determined by the BIACORE™ chip assay for affinity, by a FACS-Scatchard analysis or other methods known in the art."

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999).

In this case, the plain, ordinary meaning of the term "an isolated antibody which has an increased affinity for a fibroblast growth factor receptor 3 (FGFR3)"

is an antibody that has relatively higher affinity for a FGFR3, as compared to that of some other ligand (e.g., antibody) that binds to the same molecule.

As previously explained, the increase in the affinity of the claimed molecule would be understood to be relative; and so without a standard for ascertaining the requisite degree to which the affinity is increased, it would not be possible to know or determine whether an antibody has the requisite increased affinity for FGFR3. See M.P.E.P. § 2173.05.

In contrast to the plain, ordinary meaning that this term would be given, Applicant has argued that the term is clearly redefined in the specification to mean that the antibody binds a soluble dimeric form of an RPTK with a strength characterized by a particular dissociation constant; however, the claims are directed to an antibody that binds a FGFR3, not a soluble dimeric form of an RPTK.

Even if "RPTK" is defined elsewhere in the specification as inclusive of FGFR3, the "FGFR3" to which the claims are directed is not necessarily soluble or dimeric; and it would be improper to read such limitations into the claims.

As such, contrary to Applicant's position, it is submitted that the specification does not *clearly* redefine the claim term, so as to put one reasonably skilled in the art on notice that Applicant intends the claim be construed using such an uncommon meaning of the term.

In accordance with M.P.E.P. § 2111.01:

> Any special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." Multiform Desiccants Inc. v. Medzam Ltd., 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998). See also Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999) and MPEP § 2173.05(a).

In addition, it is aptly noted that elsewhere the specification, at, e.g., paragraph [0159] of the published application, there are disclosures that do not support the departure from common usage of the claim term. Moreover, such disclosures would not lead one to interpret the term as it appears in the claim in

such uncommon way, but would instead lead one toward construing the claim in view of its plain, ordinary meaning.

Paragraph [0159], for example, discloses:

> Moreover, affinity maturation (i.e., *increasing the affinity*[2] and specificity) of recombinant antibodies is very simple and relatively fast.

Since one of skill in the art would understand that affinity maturation involves altering the structure of an antibody with the objective of increasing its affinity, as compared to antibodies of lower affinity[3], one of skill in the art would not understand that the specification has clearly redefined the term "increased affinity" as Applicant asserts.

M.P.E.P. § 2171 states:

> There are two separate requirements set forth in this paragraph:
>
> (A) the claims must set forth the subject matter that applicants regard as their invention; and
>
> (B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.
>
> The first requirement is a subjective one because it is dependent on what the applicants for a patent regard as their invention. The second requirement is an objective one because it is not dependent on the views of applicant or any particular individual, but is evaluated in the context of whether the claim is definite — i.e., whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art.
>
> Although an essential purpose of the examination process is to determine whether or not the claims define an invention that is both novel and nonobvious over the prior art, another essential purpose of patent examination is to determine whether or not the claims are precise, clear, correct, and unambiguous. The uncertainties of claim scope should be removed, as much as possible, during the examination process.

For these reasons and after careful and complete consideration of Applicants response, it is maintained that the claims fail to delineate the metes

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[2] Emphasis added

[3] See e.g., Antibody Engineering, Second Edition (Ed. Borrebaeck; 1995; Oxford University Press: New York; pages 102-103) which teaches that *in vitro* affinity maturation processes have "been used to increase the affinity of an anti-progesterone antibody 13 to 30-fold[56] and to increase the affinity of an anti-4-hydroxy-5-iodo-3-nitrophenyl acetyl caproic acid antibody 4-fold[70]"

and bounds of the subject matter regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

It is suggested that this issue might be remedied by amending claim 1 to recite, for example, "[...] an isolated antibody which binds to a soluble, dimeric fibroblast growth factor receptor 3 (FGFR3) with a K_D of less than about 50 nM", provided that there is in fact some nexus between the "RPTK", as recited in the specification at paragraph [0135] of the published application, and "a fibroblast growth factor receptor 3 (FGFR3)".

(b) Claims 1, 6-10, 15, 22 and 31 are indefinite because of the use of the term "fibroblast growth factor receptor 3 (FGFR3)" in claim 1.

At page 12 of the response filed October 30, 2007, Applicant has argued that the recitation of FGFR3 is definite because all FGF receptors share striking similarities both structurally and functionally.

In response, as set forth in the previous office action, Webster et al (of record) teach that the term FGFR3 refers to at least 16 structurally and functionally distinct fibroblast growth factor receptors as 16 different single amino acid substitutions have been identified in FGFR3 that result in multiple different diseases. Notably, for example, Webster et al teach that FGFR3 with a Lys650Glu substitution causes a syndrome named Thanatophoric dysplasia type II, while FGFR3 with a Lys650Met substitution causes a distinct syndrome named Novel skeletal dyslplasia (e.g., page 179, Table 1). Therefore, it is apparent that due to these structural differences antibodies with "increased affinity" for one FGFR3 polypeptide, would not necessarily have "increased affinity" for other FGFR3 polypeptides. Accordingly, because it is unclear or cannot be ascertained to which of the different proteins termed "FGFR3" the antibody must have increased affinity for, it is submitted that the metes and bounds of the subject matter that is regarded as the invention is not delineated

with the clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as permit the skilled artisan to know or determine infringing subject matter.

It is suggested that this issue be remedied by amending claim 1 to recite a limitation requiring the "FGFR3", to comprise a particular amino acid sequence, which is disclosed in the specification, as filed, because such a limitation would serve to unambiguously identify the protein to which the claim is directed.

For these reasons and after careful and complete consideration of Applicants response, it is maintained that the claims fail to delineate the metes and bounds of the subject matter regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

(c) Claims 6-10 are indefinite because of the recitation that the "molecule blocks *constitutive* activation" (italicized for emphasis) in claim 6.

Starting at page 13 of the response filed October 30, 2007, Applicant has argued that the recitation of said "molecule blocks *constitutive* activation" is definite because Applicant has surprising found that the *activity* of constitutively active receptors can be blocked by molecules disclosed in the specification.

In response, the claims are not drawn to a molecule that blocks the *activity* of a constitutively active FGFR3, but a molecule which blocks *constitutive activation* of a FGFR3. Accordingly, it is immaterial if antibodies are disclosed in the specification which block the *activity* of a constitutively active FGFR3. Once again, how does one block the activation of a FGFR3 that is always active?

For these reasons and after careful and complete consideration of Applicants response, it is maintained that the claims fail to delineate the metes and bounds of the subject matter regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112,

second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. The rejection of claims 1, 6, 8-10, 15, 22 and 31 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

Starting at page 13 of the amendment filed October 30, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but are not found persuasive for the following reasons:

Again, the considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

As amended, claims 1, 6-10, 15, 22 and 31 are drawn to a structurally and functionally diverse genus of "molecules comprising the antigen-binding portion of an isolated antibody which has increased affinity for a structurally and functionally diverse genus of fibroblast growth factor receptor 3 (FGFR3) polypeptides and which block activation of said FGFR3 polypeptides", which do

not necessarily specifically bind and block the activation of any particular FGFR3 polypeptide and do not necessarily comprise the variable heavy chain amino acid sequence of SEQ ID: 106 and the variable light chain amino acid sequence of SEQ ID NO:95. Due to the indefinite nature of antibodies that have increased affinity for FGFR3, the claims are being interpreted as encompassing antibodies that specifically bind FGFR3[4]. Furthermore, due to the indefinite nature of blocking the *constitutive* activation of an FGFR3 that is always active, the claims are interpreted are being drawn to antibodies that block the ligand-dependent activation of FGFR3.

At page 13, Applicant appears to be arguing that the claims satisfy the written description requirement because the claims "are drawn to a structurally and functionally defined molecules comprising the antigen-binding portion of an isolated antibody which has increased affinity for a fibroblast growth factor receptor such as FGFR3 and which blocks activation of said fibroblast growth factor receptor". Moreover, the applicant appears to be arguing that the claimed molecules are adequately described because the molecules disclosed in Table 1F are representative of the claimed molecules.

In response, as set forth in the previous office action at page 12 the specification teaches that FGF receptors include multiple splice variants and that there are multiple different mutations that are known to occur in FGFR3 which result in a receptor that is constitutively active. Furthermore, as evidenced by Webster et al (of record) in the previous Office action, different mutations in FGFR3 are known to occur in the extracellular domain, in the transmembrane domain or in the intercellular kinase domain which result in structurally different FGFR3 polypeptides that are constitutively active. Notably, as evidenced by Trudel et al (of record) in the previous office action these structural differences provide evidence that the claimed genus of "molecules comprising the antigen-binding portion of an isolated antibody which has increased affinity for a

[4] One of skill in the art would immediately recognize that antibodies which specifically bind to a FGFR3 polypeptide have increased affinity for the FGFR3 polypeptide compared to a polypeptide

structurally and functionally diverse genus of fibroblast growth factor receptor 3 (FGFR3) polypeptides and which block activation of said FGFR3 polypeptides" is not adequately described because Trudel et al teach an FGFR3 neutralizing antibody which inhibits the ligand-dependent activity of a wild-type FGFR3 polypeptide and the activity of a constitutively active 375C FGFR3 polypeptide, but not the activity of a constitutively active K650E FGFR3 polypeptide (see e.g., page 4044). Notably, while the Applicant asserts at page 13, 3rd new paragraph that the "molecules of the present invention are capable of blocking the function of these receptors regardless where the mutation is located in the FGFR3 receptor", the specification does not support such an assertion because it teaches at page 51 that of the antibodies tested only MS-PRO 12 and 59 inhibited the activity of a FGFR3 achondroplasia mutant polypeptide.

Accordingly, the teachings of Skolnick et al, Jones and Tosatto et al (all of record) cited in the previous office action are particularly relevant in this case, because not only would one of skill in the art be unable to predict the structure and function of the "FGFR3 polypeptides" encompassed by this genus, but they would also be unable to predict if an antibody raised against one FGFR3 polypeptide would specifically recognize any other FGFR3 polypeptide, or *arguendo*, if it did, whether the antibody would block activation of any other FGFR3 polypeptide. Accordingly, it light of the disclosure presented in the specification, one of skill in the art would not be able to immediately envision, recognize or predict the structure and function of the "FGFR3 polypeptides" or which molecules comprising the antigen binding portion of an antibody with increased affinity for one FGFR3 polypeptide would have increased affinity for any other polypeptide. Notably, as set forth in the previous office action, antibodies which bind to the fibroblast growth factor receptor 3 polypeptide comprising SEQ ID NO:1, wherein the antibody comprises the variable heavy chain amino acid sequence of SEQ ID: 106 and the variable light chain amino acid sequence of SEQ ID NO:95 and block the ligand-dependent activation of

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specific for a different antigen

said fibroblast growth factor receptor 3 polypeptide (see page 51 and Figure 17, which disclose that the MSPRO59 antibody inhibits ligand-dependent activation of wild-type FGFR3 and Table 1F which discloses that the MSPRO antibody comprises the amino acid sequences of SEQ ID NO:106 and SEQ ID NO:95), would not be considered representative of the genus of structurally and functionally diverse antibodies encompassed by the claims as one of skill in the art would not recognize which FGFR3 polypeptides this antibody would have increased affinity for or that this antibody would block *activation* of FGFR3 polypeptides that undergo a mutation to become constitutively active.

Finally, Applicant has argued on page 14 of the response filed October 30, 2007 that there is no need to disclose the other four CDR regions of the antibody because the specification provides clear guidance for one of skill in the art to use the CDR3 regions by grafting in paragraph [0149] of the published Application.

In response, paragraph [0149] of the published Application generically discloses that "CDR grafting may be performed to alter certain properties of the antibody molecule including affinity or specificity"; without providing any specific disclosure of how grafting the variable heavy chain CDR3 region and the variable light chain CDR3 region describes the antigen-binding portion of an antibody. As evidenced by Mariuzza et al (of record) at page 15 of the previous office action, the antigen-binding portion of an antibody comprises six CDRs, three each from the light and heavy chain. Accordingly, without a description of those six CDRs, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish members of the genus from other antibodies.

Accordingly, after careful and complete consideration of Applicant's arguments, for these reasons and as explained more fully in the Office action mailed July 25, 2007, the specification as filed does not adequately describe the claimed invention and this rejection is maintained.

15. The rejection of claims 1, 6-10, 15, 22 and 31 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and**

using antibodies that specifically bind to the fibroblast growth factor receptor 3 (FGFR3) polypeptide comprising SEQ ID NO:1, wherein the antibody comprises the 6 CDRs from the variable heavy chain region of SEQ ID NO:106 and the variable light chain region of SEQ ID NO:95 and blocks the ligand-dependent activation of said FGFR3 polypeptide, and **while being enabling for making and using** antibodies encompassed by the claims, which are taught by the prior art, **does not reasonably provide enablement for making and using** all molecules encompassed by the full scope of the claims, for example, antibodies that specifically bind the constitutively active fibroblast growth factor receptor 3 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 but for the substitution of glycine at position 380 by arginine, wherein the antibody comprises the variable heavy chain region of SEQ ID NO:106 and the variable light chain region of SEQ ID NO:95, so as to block the ligand-dependent activation of said FGFR3 polypeptide, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

At page 14 of the response filed October 30, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments traversing the ground of rejection set forth in the preceding Office action have been carefully considered but not found persuasive to obviate this rejection.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).
The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the above rejection of the claims, as failing to comply with the written description requirement, the claims are herein drawn to molecules comprising antigen binding portions of an isolated antibody which specifically bind any fibroblast growth factor receptor 3 and which blocks activation of said fibroblast growth factor receptor 3 and such molecules that do not necessarily contain six CDRs of an antibody.

At page 14 Applicant has argued "that Examples 1-5 provide step for step guidance for one of skilled in the art to generate and verify antibodies against any FGFR3 mutations" and that Examples 6, 10 and 13 demonstrate both the in vivo and in vitro functions of the molecules of the present invention. Finally, Applicant submits that "the Examiner's allegation that FGFR3 G380C is the only mutation disclosed in the application is clearly erroneous".

In response, the claims are not drawn to molecules that comprise antigen binding portions of antibodies that specifically bind to any particular FGFR3

polypeptide, but to molecules that comprise antigen binding portions of antibodies that specifically bind to any FGFR3 polypeptide and which block activation of said FGFR3. Notably, as set forth in the previous office action at page 21, such FGFR3 polypeptides include FGFR3 polypeptides that can be *activated* by mutation, an example of which is a Glycine 380 to Arginine substitution in FGFR3. Thus the previous office action states, "[t]herefore, it is apparent that the FGFR3 polypeptide can be activated by mutations as well as by ligands, yet the specification fails to teach how to make antibodies that block the activation of FGFR3 receptors caused by mutations as the specification does not teach any antibodies that block mutations in the FGFR3 polypeptide that result in constitutive kinase activity." Therefore, it is apparent that the Examiner was using the FGFR3 Glycine 380 to Arginine substitution polypeptide as an example to illustrate why the claimed invention was not enabled and that the Examiner was not implying that this was the only mutation disclosed in the application.

Furthermore, the Examiner submits that after reviewing examples 1-5, 6, 10 and 13, it is apparent that none of these examples teach one of skill in the art how to make antibodies that block constitutive activation of any FGFR3 polypeptide. For example, where in the specification does it teach one of skill in the art how to make an antibody that prevents a FGFR3 polypeptide from mutating into a constitutively active FGFR3 polypeptide? Accordingly, one of skill in the art would be subject to undue experimentation to make antibodies that block constitutive activation of any FGFR3 polypeptide.

Finally, the Examiner notes that Applicant does not appear to present arguments or evidence that pertain to the undue experimentation that would be required by one of skill in the art to identify other FGFR3 polypeptides whose activation could be inhibited with the claimed antibodies or the undue experimentation that would be required for one of skill in the art to make antibodies comprising only heavy and light chain CDR3 regions from an antibody

which has the same functions as the parent antibody. Accordingly, the Examiner maintains that the claimed inventions are not enabled for these reasons as well.

Therefore, for these reasons and as explained more fully in the previous Office action, upon careful and complete consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) and after careful and complete consideration of Applicant's response and arguments, the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. The rejection of claims 1, 6, 10, 15 and 22 under 35 U.S.C. 102(b), as being anticipated by Cappellen et al (of record), is maintained.

At page 14 of the amendment filed October 30, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:.

Applicant has argued that while Cappellen et al teach FGFR3 specific antibodies, Cappellen et al do not teach FGFR3 antibodies with "increased affinity" for FGFR3, which Applicant submits "is a specifically defined

characteristics of molecules of the present invention, having a KD of less than about 50 nM, preferably less than about 30 nM and more preferably less than about 10 nM."

In response, as explained in the above rejection of the claims under 112, second paragraph, one of skill in the art would not understand that the specification has clearly redefined the term "increased affinity" as Applicant asserts. This is apparent because the specification discloses in paragraph [0159] of the published application that affinity maturation can be used to increase the affinity of an antibody, which one of skill in the art would understand to be an increase in antibody affinity compared to a lower starting affinity. Furthermore, because of the indefinite nature of antibodies that have increased affinity for FGFR3, the claims are being interpreted as encompassing antibodies that specifically bind FGFR3[5]; as explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, it is not apparent, nor can it be ascertained to what, if any extent the affinity of the antibody is necessarily increased relative to any other antibody because the standard for comparison is not defined in the claim or in the disclosure.

Therefore, because Cappellen et al teach antibodies specific for a FGFR3 polypeptide which are materially and structurally indistinguishable from the instantly claimed antibodies and because Applicant has not established any difference between the claimed antibodies and the antibodies of Cappellen et al, this rejection is being properly maintained. Notably, since the Patent and Trademark Office does not have the facilities for examining and comparing the inhibitory FGFR3 antibodies of Cappellen et al with that of the instant application, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibodies and the antibodies of the prior art. See *In re Best*, 562 F.2d 1252, 195 U.S.P.Q.

[5] One of skill in the art would understand specific antibodies to have increased affinity compared to non-specific antibodies

430 (CCPA 197) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

In further response, this position is deemed reasonable upon consideration of the fact that the prior art teaches antibodies that bind to a FGFR3, where according to Cellular and Molecular Immunology[6], antibodies specific for an antigen of interest have a binding constant (Kd) that usually varies from about 10^{-7} M to 10^{-11} M (page 54). Without intending to acquiesce to Applicant's position, *arguendo*, if the claims were properly construed to include any molecule comprising an antigen-binding portion of an antibody that binds to a FGFR3 with a Kd of less than about 50 nM (i.e., 50 x 10^{-9} M), it is reasonably expected, absent a showing otherwise, that the antibody disclosed by the prior art would anticipate such antibodies.

For these reasons and as explained more fully in the previous Office action, the Examiner disagrees with Applicant's contentions that the rejection should be withdrawn and the rejection of Claims 1, 6, 10, 15 and 22 under 35 U.S.C. 102(b) as being anticipated by Cappellen et al, is maintained.

18. The rejection of claims 1, 6, 10, 15 and 22 under 35 U.S.C. 102(b), as being anticipated by Johnston et al (of record) as evidenced by Chellaiah et al (of record), is maintained.

At page 15 of the amendment filed October 30, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that while Johnston et al teach FGFR3 antibodies specific for the Ig II extracellular domain of FGFR3, Johnston et al do not teach antibodies with "increased affinity" for FGFR3.

In response, as explained in the above rejection of the claims under 112, second paragraph, one of skill in the art would not understand that the

specification has clearly redefined the term "increased affinity" as Applicant asserts. This is apparent because the specification discloses in paragraph [0159] of the published application that affinity maturation can be used to increase the affinity of an antibody, which one of skill in the art would understand to be an increase in antibody affinity compared to a lower starting affinity. Furthermore, because of the indefinite nature of antibodies that have increased affinity for FGFR3, the claims are being interpreted as encompassing antibodies that specifically bind FGFR3[7]; as explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, it is not apparent, nor can it be ascertained to what, if any extent the affinity of the antibody is necessarily increased relative to any other antibody because the standard for comparison is not defined in the claim or in the disclosure.

Therefore, because Johnston et al as evidenced by Chellaiah et al teach antibodies specific for a FGFR3 polypeptide which are materially and structurally indistinguishable from the instantly claimed antibodies and because Applicant has not established any difference between the claimed antibodies and the antibodies of Johnston et al, this rejection is being properly maintained. Notably, since the Patent and Trademark Office does not have the facilities for examining and comparing the FGFR3 antibodies of Johnston et al with that of the instant application, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibodies and the antibodies of the prior art. See *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

In further response, this position is deemed reasonable upon consideration of the fact that the prior art teaches antibodies that bind to a FGFR3, where according to Cellular and Molecular Immunology[8], antibodies

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[6] (Eds. Abass et al.; 1991; W.B. Saunders: Philadelphia; page 54)
[7] One of skill in the art would understand specific antibodies to have increased affinity compared to non-specific antibodies
[8] (Eds. Abass et al.; 1991; W.B. Saunders: Philadelphia; page 54)

specific for an antigen of interest have a binding constant (Kd) that usually varies from about 10^{-7} M to 10^{-11} M (page 54). Without intending to acquiesce to Applicant's position, *arguendo*, if the claims were properly construed to include any molecule comprising an antigen-binding portion of an antibody that binds to a FGFR3 with a Kd of less than about 50 nM (i.e., 50 x 10^{-9} M), it is reasonably expected, absent a showing otherwise, that the antibody disclosed by the prior art would anticipate such antibodies.

For these reasons and as explained more fully in the previous Office action, the Examiner disagrees with Applicant's contentions that the rejection should be withdrawn and the rejection of Claims 1, 6, 10, 15 and 22 under 35 U.S.C. 102(b) as being anticipated by Johnston et al as evidenced by Chellaiah et al, is maintained.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

20. The rejection of claims 1 and 31 under 35 U.S.C. 103(a) as being unpatentable over Cappellen et al (of record), in view of US Patent 5,843,450 (of record), is maintained.

At page 15 of the amendment filed October 30, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant appears to be referencing their argument on page 14 in response to the 102 rejection over Cappellen et al, which argues that Cappellen et al do not teach FGFR3 antibodies with "increased affinity". Therefore, Applicant appears to be arguing that the combination of Cappellen and US Patent 5,843,450 cannot render the instant claims obvious.

In response, as submitted above, the 102 rejection over Cappellen et al is being properly maintained. Accordingly, the Examiner maintains that this rejection is also being properly maintained as the combination of Cappellen and US Patent 5,843,450 renders the instant claims obvious as explained in the previous office action.

For these reasons and as explained more fully in the previous Office action, the Examiner disagrees with Applicant's contentions that the rejection should be withdrawn and the rejection of Claims 1 and 31 under 35 U.S.C. 103(a) as being unpatentable Cappellen et al, in view of US Patent 5,843,450, is maintained.

21. The rejection of claims 1 and 31 under 35 U.S.C. 103(a) as being unpatentable over Johnston et al (of record), in view of US Patent 5,843,450 (of record), is maintained.

At page 15 of the amendment filed October 30, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that for the same reasons presented for the combination of Cappellen and Dawson, that this rejection should be withdrawn.

In response, as submitted above, the 102 rejections over Cappellen et al and Johnston el are being properly maintained. Accordingly, the Examiner maintains that this rejection is also being properly maintained as the combination of Johnston and US Patent 5,843,450 renders the instant claims obvious as explained in the previous office action.

For these reasons and as explained more fully in the previous Office action, the Examiner disagrees with Applicant's contentions that the rejection should be withdrawn and the rejection of Claims 1 and 31 under 35 U.S.C. 103(a) as being unpatentable Johnston et al, in view of US Patent 5,843,450, is maintained.

Conclusion

22. No claims are allowed.

23. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Williams et al (US Patent, 5707,632, published 1998, IDS filed 12/15/2003) teach fibroblast growth factor receptor polypeptides and polyclonal antibodies that specifically bind said polypeptides.

24. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory

period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner, Art Unit 1643

bd
January 19, 2008